Alkylaminoalkyl Esters of Aminonaphthoic Acids as Local Anesthetics

A DISSERTATION

SUBMITTED TO THE HORACE H. RACKHAM SCHOOL OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE UNIVERSITY OF MICHIGAN

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Alkylaminoalkyl Esters of Aminonaphthoic Acids as Local Anesthetics[1,2]

By F. F. Blicke and H. C. Parke

Ever since the discovery of novocaine,[3] attempts have been made to find a local anesthetic which will possess not only all of the favorable properties of this substance but which will exhibit, in addition, vasoconstrictor activity and anesthetize, effectively, mucous membranes when applied topically. Naturally, an increase in anesthetic action and a decrease in toxicity is sought also.[4]

Several years ago a study of alkylaminoalkyl esters of aminonaphthoic acids was begun since naphthyl analogs of novocaine had not been described in the literature. In this paper we have described esters which represent combinations of eight different dialkylamino alcohols with 3-, 4-, 5- and 6-amino-1-naphthoic acid.

Pharmacological tests, conducted by Mr. L. W. Rowe in the Parke, Davis and Company Laboratories, have shown that all of the esters which have been prepared possess definite local anesthetic power when tested in the form of their salts.[5] However, some of the hydrochlorides are quite irritating and are rather insoluble in water.

The dialkylaminoalkyl esters were prepared by

(1) This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by H. C. Parke in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) We wish to express our indebtedness to Parke, Davis and Company, whose support made this investigation possible.

(3) Einhorn, *Ann.*, **371**, 162 (1909).

(4) Recent articles on local anesthetics of the novocaine type are those of Sergievskava and Nesvad'ba [*J. Gen. Chem.* (U. S. S. R.), **8**, 924 (1938); *C. A.*, **33**, 1307 (1939)] and Burnett, Jenkins, Peet, Dreger and Adams, This Journal, **59**, 2248 (1937). We also wish to call attention to the excellent summary on local anesthetics by Elton S. Cook, *Studies of the Institutum Divi Thomae*, **2**, 63 (1938).

(5) A detailed pharmacological report will be published in another journal.

TABLE I

NITRO-1-NAPHTHOYL CHLORIDES

Compounds 1 and 4 were recrystallized from benzene, compounds 2 and 3 from petroleum ether (90–100°).

	Chloride	M. p., °C.	B. p. °C.	Mm.	Formula	Chlorine, % Calcd.	Found
1	3-Nitro[a]	137–139	205–206	12	$C_{11}H_6O_3NCl$	15.07	15.05
2	4-Nitro	95–96[b]	208–210	17[b]	$C_{11}H_6O_3NCl$	15.07	14.90
3	5-Nitro	132–134	214–217	18	$C_{11}H_6O_3NCl$	15.07	14.96
4	6-Nitro	154–155			$C_{11}H_6O_3NCl$	15.07	14.82

[a] This compound was mentioned but not described by Leuck, Perkins and Whitmore [THIS JOURNAL, **51**, 1834 (1929)]. [b] S. I. Sergievskaya and Nesvad'ba[4] reported the same melting point and recorded the boiling point as 170–171° under 5–6 mm. pressure.

condensation of the nitro-1-naphthoyl chloride with the required dialkylamino alcohol and reduction of the nitro group in the nitro ester with stannous chloride.

It was surprising to find that, with a few exceptions, the hydrochlorides of the nitro esters are colorless while a number of the corresponding salts of the amino esters are light or lemon-yellow.

We are continuing this investigation.

Experimental Part

Nitro-1-naphthoic Acids.—3-Nitronaphthalic anhydride, obtained by nitration of naphthalic anhydride,[6] was mercurated[6b] and the mixture of anhydro-3-nitro-8-hydroxymercuri-1-naphthoic acid and the corresponding 6-nitro acid treated with hydrochloric acid, whereupon 3-nitro- and a small amount of 6-nitro-1-naphthoic acid were obtained.

Acenaphthene was nitrated and then oxidized to 4-nitronaphthalic anhydride.[6a] The latter was mercurated[6b] and the mercury removed from the mixture of mercurated products with hydrochloric acid; 4-nitro- and a very small quantity of 5-nitro-1-naphthoic acid were produced.

Nitration of 1-naphthoic acid[7] yielded a mixture of 5-nitro- and 8-nitro-1-naphthoic acid.[8] A partial separation of the acids was effected by the use of hot alcohol and the 5-nitro acid was then obtained in pure form by preparation of the methyl ester and hydrolysis of the latter.

A mixture of 40 g. of the impure yellow 5-nitro-1-naphthoic acid (m. p. 227–232°) and 500 cc. of methyl alcohol was partly saturated with hydrogen chloride, heated for twelve hours on a steam-bath, the excess alcohol removed, the residue washed with sodium carbonate solution and the ester recrystallized three times from methyl alcohol. The colorless product melted at 110–111°.[9]

Twenty-five grams of the ester was heated on a steam-bath with 300 cc. of acetic acid, 100 cc. of hydrochloric acid and 100 cc. of water. The ester soon dissolved. After twelve hours the acid which had separated was removed by filtration and the filtrate concentrated. The slightly yellow product melted at 239–240°.[10]

Nitro-1-naphthoyl Chlorides.—In the case of compounds 1, 2 and 3 (Table I) the nitro acid was heated with approximately three times the calcd. amount of thionyl chloride (practical) in an oil-bath at 150° for about five hours.[11] A clear solution was obtained. The excess thionyl chloride was removed under diminished pressure and the crystalline residue distilled under diminished pressure. The acid chlorides can also be purified by recrystallization.

In the case of compound 4, pure thionyl chloride was used. Solid material was present in the reaction flask during the whole procedure and no complete solution was obtained.

Hydrochloride of Dialkylaminoalkyl Esters of Nitro-1-naphthoic Acids.—Twelve grams (0.05 mole) of the acid chloride was dissolved in 65 cc. of hot, dry benzene and 0.05 mole of the required amino alcohol added slowly through a condenser. The mixture was heated for two to four hours on a steam-bath. In some instances a precipitate formed immediately, in others a clear solution was obtained. The mixture was cooled and any crystalline hydrochloride removed by filtration. In the event that the product did not separate it was precipitated by the addition of petroleum ether (30–60°). The material was purified by recrystallization.

Monohydrochloride of Dialkylaminoalkyl Esters of Amino-1-naphthoic Acids.—Two hundredths mole of the hydrochloride of the nitro ester was dissolved or suspended in 12–35 cc. of acetic acid and 14 g. of powdered stannous chloride dihydrate added. In some cases the mixture suddenly became very hot and the stannous chloride dissolved; in such instances the mixture must be cooled rapidly. A rapid stream of dry hydrogen chloride was passed into the mixture, which was shaken or stirred, protected from moisture and maintained at 40–50°. Any undissolved stannous chloride soon disappeared. After the mixture had been saturated with hydrogen chloride, it was allowed to remain at room temperature for two hours. In many instances the tin salt addition product of the hydrochloride of the amino ester precipitated from the turbid solution[12] in crystalline form. This can be

(6) (a) Graebe and Briones, *Ann.*, **327**, 80, 84 (1903); (b) Leuck, Perkins and Whitmore, THIS JOURNAL, **51**, 1833 (1929).

(7) 1-Naphthoic acid can be obtained in very good yield by the use of solid carbon dioxide. 1-Naphthylmagnesium bromide was prepared from 36 g. of magnesium, 800 cc. of ether and 210 cc. of 1-bromonaphthalene. After the addition of 400 cc. of dry benzene, 400–500 g. of solid carbon dioxide, sawed in the form of long rods, was introduced into the mixture; yield of acid 85–90%.

(8) Eckstrand, *J. prakt. Chem.*, **38**, 156, 241 (1888).

(9) Prepared by a different method Graeff [*Ber.*, **16**, 2252 (1883)] found the melting point to be 109–110°.

(10) Eckstrand[8] reported 239°.

(11) Red rubber stoppers should be used.

(12) In a few cases the material did not dissolve and was converted into a gummy product. The latter was allowed to remain in the mixture for twelve hours, whereupon it became crystalline.

separated by filtration through a Jena filter or the whole reaction mixture can be dissolved in 50 cc. of water and then made alkaline with 10% sodium hydroxide solution; during this process the mixture should be kept cold. The

TABLE II

HYDROCHLORIDES OF ESTERS OF 3-, 4-, 5- AND 6-NITRO-1-NAPHTHOIC ACID

The hydrochlorides were recrystallized in the following manner: compounds 1, 4, 6, 7, 11, 15, 17 and 21 from alcohol; compounds 2 and 16 from dilute alcohol; compounds 3, 5, 8 and 12 from benzene; compound 19 from butyl alcohol; compounds 10, 18 and 20 from ethyl acetate and compounds 9, 13 and 14 from a mixture of ethyl acetate and acetic acid. The base of compound 1 melted at 39–41° after recrystallization from petroleum ether and the yellow base of compound 6 at 114–115° after recrystallization from absolute alcohol.

	Esters of 3-nitro-1-naphthoic acid	M. p., °C.	Formula	Chlorine, % Calcd.	Found
1	β-Diethylaminoethyl	211–213	$C_{17}H_{21}O_4N_2Cl$	10.06	10.04
2	β-Di-*n*-butylaminoethyl	169–170	$C_{21}H_{29}O_4N_2Cl$	8.67	8.62
3	β-Di-*n*-butylaminopropyl	149–150	$C_{22}H_{31}O_4N_2Cl$	8.38	8.45
4	γ-Diethylaminopropyl	203–204	$C_{18}H_{23}O_4N_2Cl$	9.67	9.78
5	γ-Di-*n*-butylaminopropyl	148–149	$C_{22}H_{31}O_4N_2Cl$	8.38	8.50
6	β,β-Dimethyl-γ-dimethylaminopropyl[a]	114–115	$C_{18}H_{23}O_4N_2Cl$	9.67	9.71
	Esters of 4-nitro-1-naphthoic acid				
7	β-Diethylaminoethyl	198–199[b]	$C_{17}H_{21}O_4N_2Cl$	10.06	10.11
8	β-Di-*n*-butylaminoethyl	76–78	$C_{21}H_{29}O_4N_2Cl$	8.67	8.69
9	β-Diethylaminopropyl	139–140	$C_{18}H_{23}O_4N_2Cl$	9.67	9.69
10	β-Di-*n*-butylaminopropyl	83–85	$C_{22}H_{31}O_4N_2Cl$	8.38	8.78
11	γ-Diethylaminopropyl	161–162	$C_{18}H_{23}O_4N_2Cl$	9.67	9.59
12	γ-Di-*n*-butylaminopropyl	117–118	$C_{22}H_{31}O_4N_2Cl$	8.38	8.47
13	β,β-Dimethyl-γ-dimethylaminopropyl[a]	150–151	$C_{18}H_{23}O_4N_2Cl$	9.67	9.86
14	β,β-Dimethyl-γ-diethylaminopropyl[c]	151–152[d]	$C_{20}H_{27}O_4N_2Cl$	8.98	9.07
	Esters of 5-nitro-1-naphthoic acid				
15	β-Diethylaminoethyl	198–199	$C_{17}H_{21}O_4N_2Cl$	10.06	10.14
16	β-Di-*n*-butylaminoethyl	131–133	$C_{21}H_{29}O_4N_2Cl$	8.67	8.50
17	β-Diethylaminopropyl	195–196	$C_{18}H_{23}O_4N_2Cl$	9.67	9.67
18	β-Di-*n*-butylaminopropyl	120–121	$C_{22}H_{31}O_4N_2Cl$	8.38	8.43
19	γ-Diethylaminopropyl	193–194	$C_{18}H_{23}O_4N_2Cl$	9.67	9.76
20	γ-Di-*n*-butylaminopropyl	118–120	$C_{22}H_{31}O_4N_2Cl$	8.38	8.46
	Ester of 6-nitro-1-naphthoic acid				
21	β-Diethylaminoethyl	184–185	$C_{17}H_{21}O_4N_2Cl$	10.06	10.08

[a] The required alcohol has been described by Mannich, Lesser and Silten [*Ber.*, **65**, 381 (1932)]; we prepared it according to the modified method of Burger [THIS JOURNAL, **60**, 1536 (1938)]. [b] Sergievskaya and Nesvad'ba [*J. Gen. Chem.* (U. S. S. R.), **8**, 929 (1938)] reported the melting point to be 189.8–190°. [c] The necessary alcohol has been prepared by Mannich, Lesser and Silten, *Ber.*, **65**, 384 (1932). [d] Sergievskaya and Nesvad'ba (ref. *b*, p. 931) reported 153–155° with decomposition.

TABLE III

MONOHYDROCHLORIDES OF ESTERS OF 3-, 4-, 5- AND 6-AMINO-1-NAPHTHOIC ACID

The hydrochlorides were recrystallized in the following manner: compounds 1, 8, 11, 13, 14, 15 and 21 from alcohol; compounds 6, 16, 17 and 19 from butyl alcohol; compounds 7, 9 and 20 from water and compounds 2, 3, 4, 5, 10, 12 and 18 from a mixture of ethyl acetate and acetic acid.

	Esters of 3-amino-1-naphthoic acid	M. p., °C.	Formula	Chlorine, % Calcd.	Found
1	β-Diethylaminoethyl	148–150	$C_{17}H_{23}O_2N_2Cl$	10.99	10.94
2	β-Di-*n*-butylaminoethyl	135–136	$C_{21}H_{31}O_2N_2Cl$	9.36	9.31
3	β-Di-*n*-butylaminopropyl	113–114	$C_{22}H_{33}O_2N_2Cl$	9.03	9.05
4	γ-Diethylaminopropyl	160–161	$C_{18}H_{25}O_2N_2Cl$	10.53	10.43
5	γ-Di-*n*-butylaminopropyl	146–147	$C_{22}H_{33}O_2N_2Cl$	9.03	8.98
6	β,β-Dimethyl-γ-dimethylaminopropyl	162–163	$C_{18}H_{26}O_2N_2Cl$	10.53	10.44
	Esters of 4-amino-1-naphthoic acid				
7	β-Diethylaminoethyl	214–216[a]	$C_{17}H_{23}O_2N_2Cl$	10.99	10.87
8	β-Di-*n*-butylaminoethyl	170–171	$C_{21}H_{31}O_2N_2Cl$	9.36	9.46
9	β-Diethylaminopropyl	197–198	$C_{18}H_{25}O_2N_2Cl$	10.53	10.56
10	β-Di-*n*-butylaminopropyl	179–180	$C_{22}H_{33}O_2N_2Cl$	9.03	9.16
11	γ-Diethylaminopropyl	184–185	$C_{18}H_{25}O_2N_2Cl$	10.53	10.49
12	γ-Di-*n*-butylaminopropyl	175–176	$C_{22}H_{33}O_2N_2Cl$	9.03	9.06
13	β,β-Dimethyl-γ-dimethylaminopropyl	219–221	$C_{18}H_{25}O_2N_2Cl$	10.53	10.51
14	β,β-Dimethyl-γ-diethylaminopropyl	184–186[b]	$C_{20}H_{29}O_2N_2Cl$	9.72	9.59

TABLE III (*Concluded*)

	Esters of 5-amino-1-naphthoic acid	M. p., °C.	Formula	Chlorine, % Calcd.	Found
15	β-Diethylaminoethyl	169–170	$C_{17}H_{23}O_2N_2Cl$	10.99	10.95
16	β-Di-*n*-butylaminoethyl	178–179	$C_{21}H_{31}O_2N_2Cl$	9.36	9.53
17	β-Diethylaminopropyl	171–172	$C_{18}H_{25}O_2N_2Cl$	10.53	10.52
18	β-Di-*n*-butylaminopropyl	157–159	$C_{22}H_{33}O_2N_2Cl$	9.03	8.87
19	γ-Diethylaminopropyl	175–177	$C_{18}H_{25}O_2N_2Cl$	10.53	10.59
20	γ-Di-*n*-butylaminopropyl	159–160	$C_{22}H_{33}O_2N_2Cl$	9.03	8.98
	Ester of 6-amino-1-naphthoic acid				
21	β-Diethylaminoethyl	169–170	$C_{17}H_{23}O_2N_2Cl$	10.99	11.08

[a] Sergievskaya and Nesvad'ba [*J. Gen. Chem.* (U. S. S. R.), **8**, 931 (1938); *C. A.*, **33**, 1307 (1939)] found 212°. [b] Ref. *a*. The melting point is reported to be 187–188°.

oily base was extracted with ether, the solution dried with fused sodium sulfate, the solvent removed and the calcd. amount of concd. hydrochloric acid added to the base. The crystalline hydrochloride formed immediately.

Summary

Esters have been prepared which represent combinations between eight different dialkylamino alcohols and 3-, 4-, 5- and 6-amino-1-naphthoic acid.

All of the esters showed decided local anesthetic activity.

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